Haddad HW, Boardman E, Williams B, Mouhaffel R, Kaye AM, Kaye AD. Combination Olanzapine and Samidorphan for the Management of Schizophrenia and Bipolar 1 Disorder in Adults: A Narrative Review. *Health Psychology Research*. 2022;10(2). doi:10.52965/001c.34224

General

Combination Olanzapine and Samidorphan for the Management of Schizophrenia and Bipolar 1 Disorder in Adults: A Narrative Review

Hannah W. Haddad[1] [a], Elena Boardman[2], Brooke Williams[2], Rama Mouhaffel[2], Adam M. Kaye, PharmD[3], Alan D. Kaye, MD, Ph.D[4]

[1] College of Medicine, Kansas City University of Medicine and Biosciences, [2] College of Medicine, Louisiana State University Health Shreveport, [3] Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, [4] Department of Anesthesiology, Louisiana State University Health Shreveport

Keywords: Schizophrenia, Bipolar Disorder, Lybalvi, samidorphan, olanzapine

https://doi.org/10.52965/001c.34224

Health Psychology Research

Vol. 10, Issue 2, 2022

Schizophrenia is a debilitating psychotic disorder characterized by positive symptoms such as delusions, hallucinations, and disorganized thoughts, and negative symptoms like lack of effect or motivation. Bipolar 1 disorder (B1D) is a psychiatric illness characterized by recurrent manic episodes in alternation with depressive episodes and interspersed periods of euthymia, ultimately resulting in psychological distress and impairment of daily functioning. Effective treatments are needed for both schizophrenia and B1D to reach the treatment goals of reducing the debilitating symptomology, improving social functioning and quality of life, and increasing the chances of recovery and more favorable long-term outcomes. To date, olanzapine is one of the most efficacious atypical antipsychotics (AAPs) for the treatment of both schizophrenia and B1D and is associated with fewer extrapyramidal effects compared to other treatments. However, compared to other AAPs, olanzapine is associated with a greater chance of metabolic syndrome, limiting its clinical use and affecting treatment compliance. Samidorphan mitigates the weight gain side effects of olanzapine by antagonizing μ-, κ-, and δ-opioid receptors. The use of combination drugs to treat psychiatric conditions is an emerging field with the goal of increasing therapeutic efficacy and decreasing undesirable side effects. Clinical trials have demonstrated combination on olanzapine and samidorphan (OLZ/SAM) treatment resulted in significantly less weight gain than olanzapine monotherapy. Clinical trial patients reported improvements in symptoms of psychosis, reduced weight gain, and overall satisfaction with their treatment. OLZ/SAM has been as shown to be a safe and effective pharmaceutical option for the clinical management of schizophrenia and B1D.

INTRODUCTION

Schizophrenia, derived from the Greek 'schizo' and 'phren' meaning 'splitting mind,' is a debilitating psychotic disorder characterized by positive symptoms such as delusions, hallucinations, and disorganized thoughts, and negative symptoms like lack of effect or motivation.[1,2] The disease has a multifactorial etiology with many associated risk factors, including maternal malnutrition, influenza during gestation, cannabis use, urbanization, and birthing complications.[1,3] The diagnosis of schizophrenia is clinical and requires the exclusion of any other potential causes of psychosis.

Although schizophrenia has a low prevalence affecting about 1% of the world's population, psychotic disorder carries a significant burden of disease.[3,4] Schizophrenia is one of the leading causes of disability and death worldwide.[3] Life expectancy is reduced by 20% in those with schizophrenia with up to 40% of schizophrenia-related deaths attributed to suicide.[1] The economic burden of the disease of schizophrenia is substantial. Annual costs are estimated to range from $94 million to $106 billion globally and more than $60 billion in the United States.[4] The economic disease

a **Corresponding author:**
Hannah W. Haddad, BS,
Kansas City University of Medicine and Biosciences
1750 Independence Ave
Kansas City, MO, 64106
Phone: (985) 788-1670
hhaddad@kansascity.edu

burden is measured in direct medical, direct nonmedical, and indirect costs, with indirect costs contributing most to the overall burden. Examples of indirect costs include unemployment, income assistance, morbidity, law enforcement, and more.[4]

Bipolar 1 disorder (B1D) is a psychiatric illness characterized by recurrent manic episodes in alternation with depressive episodes and interspersed periods of euthymia, ultimately resulting in psychological distress and impairment of daily functioning.[5] While the basis of B1D has been identified as largely biological, the disease course and symptomology can vary greatly depending on psychological, and environmental social factors.[6,7] Identified risk factors for B1D include pre-existing anxiety and disruptive behavioral disorders, maternal influenza infection, preterm birth, head injury, and physical or sexual abuse.[8] The lifetime and 12-month prevalence rates for B1D are estimated to be 2.4% and 1.5%, respectively.[5]

B1D has a high comorbidity association with both chronic medical conditions and other psychiatric conditions, resulting in an increased burden of disease and worsened prognosis. Common comorbidities include anxiety, substance abuse, personality disorders, metabolic syndrome, migraine, and obesity.[5] Consequently, those with B1D are at much higher risk for premature death with an estimated loss of 10-20 potential years of life, with suicide or cardiovascular disease being the most common causes of death.[9]

The current estimated economic burden of bipolar disease in the United States is more than $195 billion annually, with 72-80% of costs being indirect rather than direct medical costs. Major drivers of the high economic burden associated with B1D include unemployment, lost work productivity for patients and caregivers, frequent psychiatric interventions, and high rate of comorbid conditions requiring clinical management.[10]

Effective treatments are needed for both schizophrenia and bipolar disorder to reach the treatment goals of reducing the debilitating symptomology, improving social functioning and quality of life, and increasing the chances of recovery.[9,11] Combination of olanzapine and samidorphan (OLZ/SAM) has been recently Food and Drug Administration (FDA) approved for the treatment of both schizophrenia and bipolar I disorder after showing statistical improvement in clinical trials.[12]

METHODS

The present investigation is a narrative review. In 2021, a comprehensive search was performed using the PubMed database for studies related to the topic of OLZ/SAM for treatment of schizophrenia and B1D. We searched the following keywords: schizophrenia, bipolar disorder, Lybalvi, olanzapine, samidorphan. Priority for inclusion was given to recent manuscripts (within the last three years), but relevant papers older than three years were also included. An attempt to search for, use, and cite primary manuscripts whenever possible was also made. This article, therefore, is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY, PRESENTATION, AND PATHOPHYSIOLOGY OF SCHIZOPHRENIA AND BIPOLAR 1 DISORDER

PREVALENCE OF SCHIZOPHRENIA

Recent studies estimate the global number of individuals with schizophrenia to be 21 million people worldwide or roughly 1% of the population.[13,14] Prevalence studies have observed no sex differences amongst those affected by schizophrenia.[14,15] Higher incidence rates are reported in African-Caribbean migrants and their descendants.[1,16]

ETIOLOGY AND RISK FACTORS OF SCHIZOPHRENIA

Schizophrenia is a heterogeneous psychiatric illness with a multifactorial cause. Factors contributing to the etiology of schizophrenia include neurobiological, genetic, psychosocial, and environmental. The neurobiological component of schizophrenia is largely related to abnormalities in neurotransmitter signaling.[1] Family and twin studies have illustrated a genetic component of schizophrenia, as well. Monozygotic twin studies have shown varying heritability rates ranging from 40%-80% with overall heritability of schizophrenia estimated to be around 80%.[13,17–19] Circumstances in which both parents are affected by schizophrenia carry an estimated 40% risk of the offspring developing schizophrenia.[1]

Certain psychosocial or environmental risk factors have a high association with the development of schizophrenia, which includes but are not limited to low birth weight, emergency cesarean section or other birthing complications, maternal infection, residing in urban areas, childhood trauma, early stress, gestational diabetes, preeclampsia, advanced paternal age, substance abuse, and comorbid psychiatric illnesses.[1,17,20,21] Recent longitudinal studies have shown a dose-effect relationship between cannabis usage and a 40% increase in the risk of development of schizophrenia.[1]

PRESENTATION OF SCHIZOPHRENIA

Schizophrenia commonly presents in early adulthood (early-onset schizophrenia) but can also present with older age (late-onset schizophrenia).[20] Symptoms are separated into categories of positive and negative symptoms. Positive symptoms include the symptoms of psychosis, delusions, and hallucinations, as well as disorganized thought and behavior. Negative symptoms include alogia, avolition, social withdrawal, deficits in executive function, and diminished or loss of emotional expression.[13] Most people suffering from schizophrenia have significant psychosocial dysfunction resulting in impairment of daily functioning in areas of work, interpersonal relations, or self-care.[13,15] In addition, those with schizophrenia are more likely to be homeless, unemployed, or live-in poverty. Finally, schizophrenia is associated with a significantly reduced life expectancy with most deaths attributable to sequelae from comorbid illnesses.[15,22]

PATHOPHYSIOLOGY OF SCHIZOPHRENIA

The idea of a genetic role in the development of schizophrenia is well-established. Genome-wide association studies have identified numerous genes implicated in the development of schizophrenia, including but not limited to neuregulin (NGR1), dysbindin (DTNBP1), and catecholamine O-methyl transferase (COMT) Val158Met polymorphism.[1,17] NGR1 is involved in glutamate signaling and brain development, DTNBP1 aids in the release of glutamate, and COMT regulate dopamine function.[1] While the aforementioned genes have been more widely studied thus far in relation to schizophrenia, genome-wide association studies have identified a total of 108 schizophrenia-associated loci.[21,23] It has been postulated that epigenetic changes in expression levels of the COMT polymorphism and other genetic polymorphisms may have a relationship between traumatic life events and the development of schizophrenia.[17,21,24,25] Further studies are currently exploring gene-environment interactions and their effect, if any, on schizophrenia. Additionally, a 22q11.2 chromosomal deletion has been discovered with a 30-40% associative risk of schizophrenia development.[13]

The neurobiological basis of schizophrenia is largely based on defective neurotransmitter signaling, specifical hyperactivity in dopaminergic, serotoninergic, and alpha-adrenergic circuits, or hypoactivity in glutaminergic and GABAergic circuits.[1] Aberrant neural circuitry as a result of defective synaptic pruning and the associated increase in gray matter loss is associated with the cognitive deficits in schizophrenia from the resultant excitatory-inhibitory imbalance.[13,26–28] Irregular dopamine signaling in mesostriatal dopamine networks is highly associated with schizophrenia.[13] Positive symptoms are likely a result of excessive dopamine activity in the mesolimbic pathway, while negative symptoms are likely a result of reduced dopamine activity in the nigrostriatal pathway.[1,29] Finally, it has been discovered that hippocampal neurons in the CA1 region have shown increased glutamatergic activity in concordance with the developmental progression of psychotic symptoms from prodromal to syndromal as observed in longitudinal studies. The glutamate-driven hypermetabolism in specific hippocampal regions ultimately leads to reduced hippocampal volume in the brains of schizophrenia patients.[30]

PREVALENCE OF BIPOLAR 1 DISORDER

B1D is an unpredictable fluctuating mood disorder that generally presents early in life with a mean onset age of 20 and of similar prevalence in men and women.[31] B1D affects an estimated 2.4% of the world's population or about 45 million people.[5,32] Current estimates indicate that bipolar disease is the 17th leading cause of global burden of disease behind schizophrenia and other psychiatric illnesses.[31]

ETIOLOGY AND RISK FACTORS OF BIPOLAR 1 DISORDER

It is well-established that bipolar disorder has a heterogeneous etiology. Factors contributing to the development of B1D include family history and genetics, along with environmental, social, neuropsychological, and biological variables. Results from twin heritability studies report the heritability of B1D at around 70%[9]; however, the development of B1D also appears to be largely dependent upon interactions between genetics and environmental risk factors and not heritability alone.[8]

While there are many risk factors associated with bipolar disorder, such as pre-existing anxiety disorders, pregnancy, and birth complications, and substance abuse, very few risk factors show strong enough specificity to unequivocally link the risk to the development of the bipolar disorder.[8] An exception is the significant relationship that exists between experiencing childhood trauma and developing B1D with earlier onset and greater severity of the disease.[17,33] Although the exact mechanism has not yet been ascertained, there are numerous working theories investigating the physiologic link between exposure to stressors during neurodevelopmental stages and the development of B1D, which will be explored further in the pathophysiology section.[33]

PRESENTATION OF BIPOLAR 1 DISORDER

Bipolar disorder has an age of onset around adolescence or early adulthood, generally after preceding subclinical symptoms have appeared. B1D presents with alternating manic and depressive episodes with euthymic episodes in between.[33] Manic episodes generally last over one week and present with characteristics such as distractibility, impulsivity, elevated mood, overconfidence, grandiosity, talkativeness, and decreased need for sleep. Depressive episodes include experiences of anhedonia, low mood, decreased energy, and feelings of hopelessness or worthlessness.[6] The culmination of symptoms presenting with B1D results in overall reduced quality of life, especially during the presence of depressive symptoms.[31,34] Patients with B1D have a significantly higher unemployment rate and divorce/separation rate as compared to the general population along with cognitive impairment affecting activities of daily living, further contributing to reduced quality of life.[31,34–36] The poor quality of life seen in patients with B1D ultimately results in reduced educational attainment and the ability to maintain employment.[31,37] B1D is currently associated with the highest suicide rate of all psychiatric illnesses with one in four individuals suffering from B1D reporting a suicide attempt, which is the largest contributor to the premature mortality seen in the disease.[38,39]

PATHOPHYSIOLOGY OF BIPOLAR 1 DISORDER

Current evidence suggests B1D is a product of a constellation of immune-mediated inflammation in combination with abnormalities in brain structure, circuitry, neurotransmitter signaling, and intrinsic activity.[40–46] Levels of immune-regulated inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and C-reactive protein (CRP) are elevated in patients with B1D, along with increased levels of CD4+ T cells in circulation, suggesting an association between a pro-inflammatory state and B1D.[40,47–56] Manic episodes specifically seem to coincide with state-dependent inflammatory activation and increased levels of the afore-

mentioned inflammatory markers as shown in a recent longitudinal study.[40,57]

Neuroimaging studies have shown gray matter abnormalities without consistency between patients with B1D; however, imaging has consistently shown reduced white matter volumes and alterations in white matter connections, especially in the cingulum, corpus callosum, frontal brain regions, and tracts connecting regions of the limbic system.[40,58–63] It is postulated that the diffuse white matter damage may be potentiated by a CD4+ T cell-mediated immune response causing cytotoxic effects.[40] The white matter effects are most consistently seen in the limbic system, which is involved in the modulation of homeostasis and neurotransmitter signaling in response to stress.[40,64,65] Additionally, increased amygdala volume and decreased hippocampal volume are consistently seen in patients with B1D.[40,41] The combination of effects observed in the limbic network localizes B1D pathophysiology to the limbic system as a result of the localized immune-mediated white matter damage.[40]

Neurochemical changes observed in patients with B1D include hyperactivity in the hypothalamus-pituitary-adrenal (HPA) axis, transient increases in dopamine and norepinephrine signaling, and changes in serotonin metabolism.[40,66,67] Much like the etiology of the white matter changes seen in BD, data suggests the neurotransmitter dysregulation is induced by the stress response and resultant immune-mediated inflammation.[40]

Abnormalities in functional connectivity have been observed in association with B1D in functional magnetic resonance imaging (MRI) studies, most often as functional disconnection the raphe nuclei involved in serotonin signaling and increased thalamus-sensorimotor network connectivity.[40,46,68,69]

Together, the data show that the pathophysiology of B1D is ultimately the result of immune dysregulation with a pro-inflammatory state causing white matter damage in the limbic system, leading to changes in neurotransmitter signaling and functional brain connectivity and activity, precipitating the presentation of the mania and depression seen in B1D.[40]

CURRENT TREATMENT OF SCHIZOPHRENIA AND BIPOLAR 1 DISORDER

CURRENT TREATMENT OF SCHIZOPHRENIA

Related to its disease complexity, there are several therapeutic options available to treat the various positive, negative, and cognitive symptoms of schizophrenia, including first-generation antipsychotics (FGAs), atypical antipsychotics (AAPs), third-generation antipsychotics, as well as other nonpharmacologic treatments such as cognitive-behavioral therapy (CBT) and exercise.[70–74]

The first pharmacologic treatments for schizophrenia were initially developed in the 1960s based on the dopamine hypothesis, which emphasized the role of excessive dopamine in the production of positive symptoms of schizophrenia.[71,74,75] The FGA chlorpromazine supports this hypothesis and was the first FDA-approved pharmacologic therapy for schizophrenia.[74,76] Chlorpromazine reduces positive symptoms by non-selectively antagonizing dopamine-2 (D_2) receptors, however, it has little effect on negative and cognitive symptoms. Chlorpromazine's lack of selectivity to dopamine receptors in the mesolimbic pathway causes many side effects including parkinsonian-like extrapyramidal effects because of D_2 receptor antagonism in the nigrostriatal pathway. The side effects of FGAs led to the development of more selective treatment options such as AAPs and third-generation antipsychotics, which each target multiple receptor types.[74,76]

AAPs differ from FGAs by exhibiting greater antagonism at serotonin ($5\text{-}HT_{2A}$) receptors than at D_2 receptors in the nigrostriatal pathway and bind with higher affinity to D_4 than D_2 receptors, resulting in a lower occurrence of extrapyramidal side effects and reduction of negative symptoms.[74] Clozapine is the only FDA-approved AAP for treatment-resistant schizophrenia, which is most commonly diagnosed when patients fail to respond to at least two other antipsychotics.[73] Clozapine, however, is associated with various autonomic side effects such as hypotension and reflex tachycardia, as well as agranulocytosis, drooling, constipation and seizures.[71,74] Olanzapine and risperidone are newer AAPs, with fewer autonomic side effects and neither are associated with agranulocytosis.[71,74,77] Third generation antipsychotics such as aripiprazole, aripiprazole, and cariprazine are newer treatments that exhibit partial agonist of the D_2 receptor.[74,78]

Other nonpharmacologic treatments of schizophrenia such as CBT and exercise, are reported to reduce negative and cognitive symptoms of schizophrenia, which can be used in conjunction with pharmacologic therapy.[72,79] Decreased hippocampal volume is associated with impairment of executive functioning and cognition in schizophrenia.[79] Pajonk et al[79] found that three months of aerobic exercise increased hippocampal volume which also correlated with increased short-term memory test scores in patients with schizophrenia. Recently, research investigating the use of combination and multi-target drug therapies to treat schizophrenia has emerged.[74] Targeting multiple neurotransmission pathways, with multiple receptors, could potentially allow for increased therapeutic efficacy and decreased unwanted side effects.

CURRENT TREATMENT OF ACUTE MANIA IN BIPOLAR 1 DISORDER

Lithium carbonate and chlorpromazine were among the first pharmacologic treatments for acute mania in B1D in the 1940s and 1950s, however the acceptance of lithium was delayed due to toxicity observed in patients given unregulated dosages.[80] Subsequently, the utilization of AAPs was also proven efficacious in the treatment of acute mania.[81] AAPs such as aripiprazole, asenapine, cariprazine, olanzapine, paliperidone, risperidone, and ziprasidone, as well as quetiapine (in higher doses), were authorized for treatment of dysphoric and mixed state mania.[82,83] Sodium divalproex (valproate) and carbamazepine are two anticonvulsants approved for the treatment of acute mania, however, they have not shown efficacy in long-term prophylaxis.[81,82]

CURRENT TREATMENT OF DEPRESSION IN BIPOLAR 1 DISORDER

In patients with B1D, several studies reported that depressive episodes account for nearly three quarters of the mean proportion of weeks ill (approximately 50%), causing depression to be a major contributor to the burden of illness in B1D.[82,84,85] Current treatments for acute depressive episodes exhibit inconsistent results, and thorough investigation into long-term prophylaxis is limited. Despite a lack of evidence showing efficacy and safety, B1D-depression is often treated with antidepressants. In this regard, some clinicians utilize antidepressants only in acute treatment of B1D-depression related to concern of induction of mood switching to hypomania, mania, and mixed states.[86]

LONG-TERM PROPHYLAXIS

Lithium has been a component of the first-line treatment of B1D for almost 60 years.[87] Along with its more prominent effects against mania and hypomania, lithium may also have long-term benefits against B1D-depression recurrence and suicide risk reduction in B1D patients.[88] Lamotrigine is an anticonvulsant that is FDA-approved for long-term B1D prophylaxis and has reportedly limited the risk of recurrence of depressive episodes, however, it lacks efficacy in managing acute mania.[89]

TREATMENT RESISTANCE BIPOLAR 1 DISORDER

For B1D patients resistant to pharmacotherapy, nonpharmacologic therapies such as transcranial magnetic stimulation could be a promising new treatment option for reducing depressive symptoms and mania. However, current studies have reported mixed results, therefore more confirmatory research is needed.[90]

OLZ/SAM DRUG INFO

OLZ/SAM, marketed as Lybalvi, became FDA-approved for the treatment of adults with schizophrenia and B1D on June 1, 2021.[91] OLZ/SAM is a daily oral tablet composed of multiple dose strengths of olanzapine, (5, 10, 15, 20 mg) depending on the disorder being treated, and a fixed dose of 10mg of samidorphan.[92] Specifically, OLZ/SAM treatment in B1D is used for acute management of manic/mixed episodes, maintenance monotherapy, or as an adjunct to lithium or valproate.[91] Olanzapine is one of the most efficacious AAPs in the treatment of both schizophrenia and B1D and is associated with fewer extrapyramidal effects than with FGA treatment.[93,94] However, compared to other AAPs, olanzapine is associated with a greater chance of metabolic abnormalities such as dyslipidemia, type II diabetes, and weight gain, limiting its clinical use and affecting treatment compliance.[93–97]

In studies enrolling healthy adults and adults with schizophrenia, the combination of olanzapine with samidorphan, a μ-opioid receptor antagonist, mitigated weight gain associated with olanzapine monotherapy.[94,98,99] The opioid system has been implicated in the role of mediating feeding behavior, food reward, and metabolism in many clinical and preclinical studies. For example, a decrease in weight gain was reported in μ-, κ-, and δ- opioid receptor knockout mice, despite no differences in caloric intake in μ- and κ-opioid receptor knockouts.[99] Therefore, antagonism of the opioid system by samidorphan was introduced to minimize olanzapine-induced weight gain and increase olanzapine's use as a treatment for schizophrenia and B1D.[94] However, although samidorphan decreases olanzapine-induced weight gain, it has not been shown to decrease any of the other metabolic adverse effects of olanzapine therapy, such as dyslipidemia and type II diabetes, potentially indicating a direct effect of olanzapine on metabolism.[94] Contraindications for OLZ/SAM include patients taking opioids, and patients going through acute opioid withdrawal.[100]

OLZ/SAM MECHANISM OF ACTION

OLZ/SAM is a novel combination of olanzapine and samidorphan, that has been reported to mitigate the weight gain seen in olanzapine monotherapy.[91] Olanzapine has already been proven to be efficacious in the treatment of schizophrenia and B1D through D_2 receptor antagonism in the mesolimbic system and 5-HT_{2A} receptor antagonism in the frontal cortex.[96,101] Antagonism of D_2 receptors decreases positive symptoms of schizophrenia while antagonism of 5-HT_{2A} receptors decreases negative symptoms.[96,101] Several MRI studies also found increased activity in the prefrontal cortex during cognitive and emotional tasks in schizophrenia patients treated by olanzapine, suggesting a pattern of positive effects on cognition as well.[102]

The role of a said orphan in OLZ/SAM is to mitigate the weight gain induced by olanzapine monotherapy.[99] Samidorphan binds with high affinity to μ-, κ-, and δ-opioid receptors and primarily functions as a μ-opioid antagonist and partial agonist at κ- and δ-opioid receptors.[98,103,104] Samidorphan has been reported to decrease activation of the mesolimbic reward system when used in combination with buprenorphine in the treatment of the major depressive disorder.[105] While the mechanism of action for reducing weight gain via samidorphan is not entirely understood, opioid receptors are present throughout the mesolimbic system and their antagonism by the μ-opioid antagonist naltrexone, is observed to reduce cravings for sweet/rich foods.[98,104] Results of a 12-week, phase-II trial, found that OLZ/SAM treatment in schizophrenia patients, is associated with significantly less weight gain than olanzapine monotherapy.[106] Therefore, samidorphan inhibition of the mesolimbic reward system by μ-opioid receptor antagonism is presumed to be the source of the observed decrease in olanzapine-induced weight gain in patients administered OLZ/SAM.[98,105]

PHARMACOKINETICS AND PHARMACODYNAMICS OF OLZ/SAM

A phase I study assessing the pharmacokinetic profile of olanzapine and samidorphan in schizophrenia patients after once-daily 14-day administration of OLZ/SAM, found that steady-state concentrations of both drugs were reached linearly after one week.[106] Olanzapine is primarily metab-

olized by cytochrome P450 (CYP) 1A2 mediated oxidation and also via direct glucuronidation by uridine 5'-diphosphate-glucuronosyltransferase 1A4.[107] Therefore, caution should be exercised with coadministration of either CYP1A2 inhibitors, such as fluvoxamine, or CYP1A2 inducers including carbamazepine or rifampin. Samidorphan is mainly metabolized by CYP3A4, consequently, caution should also be taken when co-administering CYP3A4 inducers and inhibitors.[107] Heavy smoking also induces CYP1A2 leading to increased clearance of olanzapine by 30-55% when compared to nonsmokers.[108]

Physiologically based and clinically developed pharmacokinetic models using healthy individuals and patients with schizophrenia, concluded that samidorphan did not alter the pharmacokinetics of olanzapine when co-administered across the clinical dose range (5-30mg), which is consistent with previously published studies.[106,107,109] A study assessing hepatic and renal impairment effects on the pharmacokinetics of olanzapine and samidorphan, reported that patients with moderate hepatic impairment experienced higher absorption and systemic exposure to olanzapine than healthy participants, and those with renal impairment had a 33% and 56% decrease in total body clearance of olanzapine and samidorphan, respectively.[110]

Olanzapine binds with high affinity at dopamine D_{1-4}, $5HT_{2a/2c}$, $5HT_6$, histamine-1 (H_1), and adrenergic-1 ($\alpha 1$) receptors.[100] Blocking dopamine receptors, increases the risk of side effects such as akathisia, extrapyramidal symptoms, tardive dyskinesia, and neuroleptic malignant syndrome.[101] Samidorphan binds with high affinity to μ-, κ-, and δ-opioid receptors, primarily functioning as a μ-opioid antagonist and κ- and δ-opioid partial agonists.[98,103,104] In a phase II study, significantly lower weight gain of about 37% was observed in patients taking OLZ/SAM compared to those treated with olanzapine monotherapy.[104]

CLINICAL STUDIES: SAFETY AND EFFICACY

OLZ/SAM has shown statistical and clinical efficacy and safety in several studies.[111] In the OLZ/SAM development program, 18 studies were used to evaluate the safety and the antipsychotic and weight-mitigating efficacy. The studies concluded the efficacy and safety of OLZ/SAM were similar to olanzapine, with reduced weight gain overall.[111]

In a recent study from 2015-2017, 401 adults with clinically diagnosed schizophrenia who were experiencing an acute episode of psychosis were administered ⩾1 dose of OLZ/SAM. Of the 401 patients, 352 patients completed the treatment. Results showed significant improvement in the Positive and Negative Syndrome Score (PANSS) and Clinical Global Impression-Severity (CGI-S) score within 4 weeks of patients receiving OLZ/SAM versus placebo. Although OLZ/SAM showed the most efficacy, it also had the highest percentage of adverse effects (54.5% vs. 44.8% in placebo) of weight gain, somnolence, dry mouth, anxiety, and headache. Overall, OLZ/SAM was well tolerated and had efficacy and safety similar to that of olanzapine.[112]

In an open-label extension study, the long-term tolerability, safety, and efficacy were evaluated in patients with schizophrenia. Semi-structured one hour-long interviews were conducted in which all 41 patients indicated their diagnosis of schizophrenia had impacted personal, social, and financial aspects of their lives. Of the 41 patients that were administered OLZ/SAM, 39 patients had reported improvements in both positive and negative symptoms of psychosis. Overall, most of the patients were satisfied with their treatment.[113]

In a 52-week open-label extension study, OLZ/SAM was concluded to improve schizophrenia symptoms, while mitigating weight-gain in patients. Of the 281 patients that enrolled, 183 patients completed the 52-week trial. PANSS total and CGI-S scores declined in all patients that completed the trial. Increases in weight gain were stabilized by week 6, with an average 2.79% increase in weight gain. Overall, OLZ/SAM was well tolerated.[114]

In a randomized, double-blind, placebo-controlled study of 106 healthy, male normal weight volunteers, OLZ/SAM was shown to have similar safety and tolerability as olanzapine. However, OLZ/SAM had less side effects such as nausea, weight gain and metabolic risk. Further studies are needed to explore the side effects and efficacy of additional doses over a longer duration of time in schizophrenic patients.[98]

In randomized, controlled trials, OLZ/SAM and olanzapine-monotherapy were compared in healthy volunteers to determine short-term weight and cardiometabolic changes in these patients. In the OLZ/SAM group, weight changes were not statistically different than the olanzapine groups. However, OLZ/SAM was found to help prevent olanzapine-induced weight gain in healthy males with a lower initial BMI. This study concludes there is not sufficient evidence that OLZ/SAM prevents olanzapine-induced weight gain and olanzapine-induced cardiometabolic abnormalities.[115]

In a 24-week phase 3 double-blind trial, OLZ/SAM was assigned to 280 patients while olanzapine-monotherapy was assigned to 281 patients. Of these patients, 538 had post-baseline weight assessments. Of these 538 patients, the least-squares mean percent weight change from baseline of OLZ/SAM patients was approximately 4.21%; the olanzapine-monotherapy group was 6.59%. In addition, schizophrenia symptom improvement was similar to the olanzapine-monotherapy treatment. This study concluded that OLZ/SAM treatment was associated with similar schizophrenia symptom improvement, but with significantly less weight gain and smaller increases in waist circumference.[116]

In a multicenter, randomized phase 2 study of OLZ/SAM, the efficacy and weight gain side effects of OLZ/SAM were observed. Seventy-five patients received olanzapine plus placebo, and the rest received OLZ/SAM in different dosages (N=80; 5 mg, N=86; 10 mg, N=68; 20 mg). Results showed that OLZ/SAM resulted in statistically significant lower weight gain compared to olanzapine plus placebo patients, with OLZ/SAM showing a 37% lower weight gain compared to olanzapine plus placebo. In addition, the safety and efficacy of OLZ/SAM had a similar profile to olanzapine plus placebo, making OLZ/SAM a better option for mitigating weight gain while simultaneously treating schizophrenia.[99]

In phase 3, a 52-week open-label extension study of OLZ/SAM in patients with schizophrenia, the safety, efficacy, tolerability, and side effects were studied. Patients were di-

vided randomly into a 24-week, double-blind phase 3 study to compare weight gain in patients administered OLZ/SAM versus olanzapine-monotherapy. Two hundred sixty-five patients were administered OLZ/SAM, with 167 completing the extension of the remaining study. Fasting lipid, glycemic parameters, and PANSS scores remained stable throughout the study in patients receiving OLZ/SAM. CGI-S scores remained 3 or less in 81.3% of the patients, indicating mild illness severity. Results indicated patients that who were administered OLZ/SAM tolerated the medication well with significant results including smaller waist circumferences, smaller weight gain, and efficacy of the medication combination.[117,118]

In an open-label, randomized study, 48 healthy, non-smoking participants were randomly assigned to either generic olanzapine-monotherapy, OLZ/SAM, or Zyprexa, brand olanzapine (B-OLZ), in a 1:1:1:1:1:1 randomization. The pharmacokinetics of the drug-drug interactions between olanzapine and samidorphan were studied. Results indicated that OLZ/SAM was not shown to have any safety concerns nor affect the pharmacokinetics and bioavailability of olanzapine. In general, OLZ/SAM was well-tolerated by patients.[119]

Because OLZ/SAM is used in both schizophrenia and B1D, medications such as lithium or valproate are commonly prescribed along with OLZ/SAM. In an open-label, single-sequence two-cohort study, 34 healthy adults were administered lithium carbonate or divalproex sodium, once every 12 hours on days 1-7. On days 8-18, participants were administered olanzapine. The safety profiles of lithium and valproate while administered with OLZ/SAM were similar to the safety profile of what was previously reported for lithium and valproate. Administration of OLZ/SAM did not have a clinically significant effect on the pharmacokinetics of lithium or valproate and was generally well-tolerated.[120]

Because OLZ/SAM has an antipsychotic component, QTc intervals should be monitored for patients on this drug. In a randomized double-blind, placebo-controlled study, 100 patients with stable schizophrenia were randomized to receive OLZ/SAM or a placebo. Electrocardiograms (ECGs) and plasma drug concentrations were observed before and after dose administration. No clinically significant QTc effects were observed between OLZ/SAM doses.[121]

Although several studies have indicated OLZ/SAM has similar improvement rates to olanzapine-monotherapy, it has not had the same results in patients with a comorbidity of alcohol use disorder (AUD). In phase 2 double-blind study, patients with schizophrenia and AUD were enrolled in a 1:1 randomized trial of OLZ/SAM and placebo. After 30-60 weeks of treatment, no significant difference was observed between schizophrenics with comorbidity of AUD treated with OLZ/SAM vs olanzapine-monotherapy.[122]

CONCLUSION

Schizophrenia and B1D are severe psychiatric illnesses with a significant economic burden of disease, high comorbidity rates, and poor prognoses despite relatively low prevalence rates.[3–5,9,10,32] Current pharmacological treatments of schizophrenia include FGAs, AAPs, and third-generation antipsychotics.[70–74] The current pharmacological treatment of B1D includes AAPs and lithium.[81,87] The use of combination drugs to treat psychiatric conditions is an emerging field with the primary goal of increasing therapeutic efficacy and decreasing undesirable side effects through targeting neurotransmission pathways.[74]

OLZ/SAM is approved by the FDA to treat schizophrenia and B1D. Olanzapine has proven effective for the treatment of schizophrenia and B1D through dopamine and serotonin receptor antagonism.[96,101] Samidorphan mitigates the weight gain side effects of olanzapine by antagonizing μ-, κ-, and δ-opioid receptors.[98,103,104] In clinical trials, OLZ/SAM showed similar efficacy in treating schizophrenia and B1D and exhibited less side effects (weight gain, somnolence, dry mouth, anxiety, headache) when compared to olanzapine-monotherapy.[112] No concerns regarding safety, pharmacokinetics, or bioavailability were identified during clinical trials.[119] Most patients reported improvements in symptoms of psychosis, reduced weight gain, and overall satisfaction with the combination treatment. OLZ/SAM has shown to be an effective and safe pharmaceutical option for the clinical management of schizophrenia and B1D.[113,116]

ACKNOWLEDGEMENTS

I would like to express my gratitude for the support and guidance provided by those in the Department of Anesthesiology at Louisiana State University Heath Shreveport.

LIST OF AUTHORS AND THEIR CONTRIBUTIONS

Haddad H (B.S.), (study design, manuscript preparation, and editing)

Boardman E (B.S.), (data analysis, manuscript preparation)

Williams B (B.S.), (data analysis, manuscript preparation)

Mouhaffel R (B.S.), (data analysis, manuscript preparation)

Kaye AM (PharmD), (data collection, manuscript preparation)

Kaye AD (MD, Ph.D.), (study design, manuscript preparation)

DISCLOSURES

The Authors did not receive any funding or financial support or potential sources of conflict of interest.

This study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

Submitted: November 25, 2021 EDT, Accepted: January 11, 2022 EDT

Table 1. Lybalvi Studies and Findings

Author and Year	Groups Studied and Intervention	Results and Findings	Conclusions
Potkin et al[112] (2020)	401 adults with clinically diagnosed schizophrenia who were experiencing an acute episode of psychosis were administered ≥1 dose of OLZ/SAM	Results indicated a significant improvement in PANSS and CGI-S total scores within 4 weeks in patients receiving OLZ/SAM versus placebo.	OLZ/SAM was well tolerated and had efficacy and safety similar to that of olanzapine-monotherapy
Simmons et al[113] (2021)	41 patients with schizophrenia whose diagnosis of schizophrenia had impacted personal, social, and financial aspects of their lives were administered OLZ/SAM	Results indicated improvements in both positive and negative symptoms of psychosis in 39 of these patients	Most of the patients were satisfied with their treatment of OLZ/SAM
Citrome et al[111] (2021)	18 studies were used to evaluate the antipsychotic and weight-mitigating efficacy and safety of OLZ/SAM in >1600 patients	Results indicated that the efficacy and safety of OLZ/SAM were similar to olanzapine, with reduced weight-gain overall	The efficacy and safety of OLZ/SAM were similar to olanzapine-monotherapy, with reduced weight-gain overall
Yagoda et al[114] (2021)	Patients with clinically diagnosed schizophrenia who completed the first phase of the ENLIGHTEN-1 study program were administered OLZ/SAM (N=277 administered ≥1 dose OLZ/SAM; N=183 completed 52 weeks of program)	Results indicated PANSS total and CGI-S scores declined in all patients that completed the trial. Increases in weight gain were stabilized by week 6, with an average 2.79% increase in weight gain	OLZ/SAM was concluded to improve schizophrenia symptoms, while mitigating weight-gain in patients
Brunette et al[122] (2020)	234 patients with schizophrenia and AUD were enrolled in a 1:1 randomized trial of OLZ/SAM and placebo	Results indicated that no significant difference was observed between schizophrenics with comorbidity of AUD treated with OLZ/SAM vs olanzapine	OLZ/SAM can be used in schizophrenics with comorbidity of AUD. However, it is not superior to olanzapine and further studies are needed
Silverman et al[98] (2018)	106 healthy, male normal weight volunteers were administered either OLZ/SAM, SAM, or placebo in a 2:2:1:1 ratio	Results indicated that OLZ/SAM was shown to have similar safety and tolerability as metabolic risk	Although OLZ/SAM had lesser side effects than olanzapine, further studies are needed in order to explore the side effects and efficacy of additional doses over a longer duration of time in schizophrenic patients
Sun et al[121] (2020)	100 patients aged 18 to 60 years with stable schizophrenia were administered either OLZ/SAM or OLZ/SAM-matched placebo in a 3:2 ratio	Results indicated there were no clinically significant QTc effects, including QT prolongation, across the OLZ/SAM doses, ranging from 110 to 160 ng/mL	OLZ/SAM has no significant effect on QT intervals
Sun et al[120] (2020)	34 healthy adults were administered lithium carbonate or divalproex sodium in a 1:1 ratio. On days 8-18, participants were administered olanzapine.	Results indicated that the safety profiles of lithium and valproate while administered with OLZ/SAM was similar to the safety profile of what was previously reported for lithium and valproate.	Administration of OLZ/SAM did not have a clinically significant effect on the pharmacokinetics of lithium or valproate and was generally well-tolerated.
Sun et al[119] (2018)	48 healthy, nonsmoking participants were randomly assigned to either olanzapine monotherapy, OLZ/SAM, or B-OLZ in a 1:1:1:1:1:1 randomization where pharmacokinetics of the drug-drug interactions between olanzapine and samidorphan were studied.	Results indicated that OLZ/SAM was shown to not have any safety concerns nor affect the pharmacokinetics and bioavailability of olanzapine monotherapy	Simultaneous administration of olanzapine and samidorphan does not affect the bioavailability of olanzapine. In general, OLZ/SAM is well-tolerated by patients
Srisurapanont et al[115] (2021)	OLZ/SAM and olanzapine administration were compared in 1195 volunteers	Results indicated that the OLZ/SAM group's weight changes were not statistically different than the olanzapine group	There is not sufficient evidence that samidorphan prevents olanzapine-induced weight gain and olanzapine-induced cardiometabolic abnormalities.

			Samidorphan was well-tolerated by the patients treated with olanzapine in this study.
Correll et al[116] (2020)	OLZ/SAM was administred to 280 patients while olanzapine was assigned to 281 patients to compare the effects of OLZ/SAM on weight gain	Results indicated that schizophrenia symptom improvement was similar to the olanzapine treatment with statistically significant weight differences	This study concluded that OLZ/SAM treatment was associated with similar schizophrenia symptom improvement, but with significantly less weight gain and smaller increases in waist circumference
Martin et al[99] (2019)	75 patients received olanzapine plus placebo, and the rest received OLZ/SAM in different dosages (N=80; 5 mg, N=86; 10 mg, N=68; 20 mg) to test OLZ/SAM weight gain mitigation	Results indicated that OLZ/SAM resulted in statistically significant lower weight gain compared to olanzapine plus placebo patients, with OLZ/SAM showing a 37% lower weight gain compared to olanzapine plus placebo.	Safety and efficacy of OLZ/SAM had a similar profile to olanzapine plus placebo, making OLZ/SAM a better option for mitigating weight gain while simultaneously treating schizophrenia
Kahn et al[117] (2021)	265 patients with schizophrenia were administered either OLZ/SAM or olanzapine to compare the efficacy, safety, tolerability, and side effects of OLZ/SAM to olanzapine	Results indicated that fasting lipid, glycemic parameters, and PANSS scores remained stable throughout the study in patients receiving OLZ/SAM. CGI-S scores remained 3 or less in 81.3% of the patients, indicating mild illness severity.	Patients that were administered OLZ/SAM tolerated the medication well with significant results including smaller waist circumferences, smaller weight gain and efficacy of the medication combination
Kahn et al[118] (2021)	167 patients with schizophrenia were administered either OLZ/SAM or olanzapine to compare the efficacy, safety, tolerability and side effects of OLZ/SAM to olanzapine	Results indicated that fasting lipid, glycemic parameters and PANSS scores remained stable throughout the study in patients receiving OLZ/SAM. CGI-S scores remained 3 or less in 81.3% of the patients, indicating mild illness severity.	Patients that were administered OLZ/SAM tolerated the medication well with significant results including smaller waist circumferences, smaller weight gain and efficacy of the medication combination

Combination olanzapine and samidorphan (OLZ/SAM); Positive and Negative Syndrome Score (PANSS); Clinical Global Impression-Severity (CGI-S); alcohol use disorder (AUD); brand- olanzapine (B-OLZ)

REFERENCES

1. Hany M, Rehman B, Azhar Y, Chapman J. Schizophrenia. In: *StatPearls*. StatPearls Publishing; 2021. Accessed September 15, 2021. http://www.ncbi.nlm.nih.gov/books/NBK539864/

2. Tandon R, Gaebel W, Barch DM, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res*. 2013;150(1):3-10. doi:10.1016/j.schres.2013.05.028

3. Marder SR, Cannon TD. Schizophrenia. Ropper AH, ed. *N Engl J Med*. 2019;381(18):1753-1761. doi:10.1056/nejmra1808803

4. Chaiyakunapruk N, Chong HY, Teoh SL, Wu DBC, Kotirum S, Chiou CF. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatr Dis Treat*. 2016;12:357-373. doi:10.2147/ndt.s96649

5. Carvalho AF, Firth J, Vieta E. Bipolar Disorder. Ropper AH, ed. *N Engl J Med*. 2020;383(1):58-66. doi:10.1056/nejmra1906193

6. Ironside ML, Johnson SL, Carver CS. Identity in bipolar disorder: self-worth and achievement. *J Pers*. 2020;88(1):45-58. doi:10.1111/jopy.12461

7. Freund N, Juckel G. Bipolar Disorder: Its Etiology and How to Model in Rodents. *Methods Mol Biol*. 2019;2011:61-77. doi:10.1007/978-1-4939-9554-7_4

8. Marangoni C, Faedda GL, Baldessarini RJ. Clinical and Environmental Risk Factors for Bipolar Disorder: Review of Prospective Studies. *Harv Rev Psychiatry*. 2018;26(1):1-7. doi:10.1097/hrp.0000000000000161

9. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841-1856. doi:10.1016/s0140-6736(20)31544-0

10. Bessonova L, Ogden K, Doane MJ, O'Sullivan AK, Tohen M. The Economic Burden of Bipolar Disorder in the United States: A Systematic Literature Review. *ClinicoEconomics Outcomes Res*. 2020;12:481-497. doi:10.2147/ceor.s259338

11. Crespo-Facorro B, Such P, Nylander AG, et al. The burden of disease in early schizophrenia – a systematic literature review. *Curr Med Res Opin*. 2021;37(1):109-121. doi:10.1080/03007995.2020.1841618

12. Paik J. Olanzapine/Samidorphan: First Approval. *Drugs*. 2021;81(12):1431-1436. doi:10.1007/s40265-021-01568-0

13. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia—An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. doi:10.1001/jamapsychiatry.2019.3360

14. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005;2(5):e141. doi:10.1371/journal.pmed.0020141

15. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull*. 2018;44(6):1195-1203. doi:10.1093/schbul/sby058

16. Messias EL, Chen CY, Eaton WW. Epidemiology of Schizophrenia: Review of Findings and Myths. *Psychiatr Clin North Am*. 2007;30(3):323-338. doi:10.1016/j.psc.2007.04.007

17. Misiak B, Stramecki F, Gawęda Ł, et al. Interactions Between Variation in Candidate Genes and Environmental Factors in the Etiology of Schizophrenia and Bipolar Disorder: a Systematic Review. *Mol Neurobiol*. 2018;55(6):5075-5100. doi:10.1007/s12035-017-0708-y

18. Cardno AG, Gottesman II. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am J Med Genet*. 2000;97(1):12-17. doi:10.1002/(sici)1096-8628(200021)97:1

19. Misiak B, Frydecka D, Rybakowski JK. Editorial: Endophenotypes for Schizophrenia and Mood Disorders: Implications from Genetic, Biochemical, Cognitive, Behavioral, and Neuroimaging Studies. *Front Psychiatry*. 2016;7. doi:10.3389/fpsyt.2016.00083

20. Chen L, Selvendra A, Stewart A, Castle D. Risk factors in early and late onset schizophrenia. *Compr Psychiatry*. 2018;80:155-162. doi:10.1016/j.comppsych.2017.09.009

21. Stilo SA, Murray RM. Non-Genetic Factors in Schizophrenia. *Curr Psychiatry Rep*. 2019;21(10):100. doi:10.1007/s11920-019-1091-3

22. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. *Annu Rev Clin Psychol*. 2014;10(1):425-448. doi:10.1146/annurev-clinpsy-032813-153657

23. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427. doi:10.1038/nature13595

24. Green MJ, Chia TY, Cairns MJ, et al. Catechol-O-methyltransferase (COMT) genotype moderates the effects of childhood trauma on cognition and symptoms in schizophrenia. *J Psychiatr Res*. 2014;49:43-50. doi:10.1016/j.jpsychires.2013.10.018

25. van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull*. 2008;34(6):1066-1082. doi:10.1093/schbul/sbn117

26. Fusar-Poli P, Radua J, McGuire P, Borgwardt S. Neuroanatomical Maps of Psychosis Onset: Voxel-wise Meta-Analysis of Antipsychotic-Naive VBM Studies. *Schizophr Bull*. 2012;38(6):1297-1307. doi:10.1093/schbul/sbr134

27. Kambeitz J, Kambeitz-Ilankovic L, Cabral C, et al. Aberrant Functional Whole-Brain Network Architecture in Patients With Schizophrenia: A Meta-analysis. *Schizophr Bull*. 2016;42(suppl 1):S13-S21. doi:10.1093/schbul/sbv174

28. Sui J, Pearlson GD, Du Y, et al. In Search of Multimodal Neuroimaging Biomarkers of Cognitive Deficits in Schizophrenia. *Biol Psychiatry*. 2015;78(11):794-804. doi:10.1016/j.biopsych.2015.02.017

29. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *P T Peer-Rev J Formul Manag*. 2014;39(9):638-645.

30. Lieberman JA, Girgis RR, Brucato G, et al. Hippocampal dysfunction in the pathophysiology of schizophrenia: a selective review and hypothesis for early detection and intervention. *Mol Psychiatry*. 2018;23(8):1764-1772. doi:10.1038/mp.2017.249

31. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. *Nat Rev Dis Primers*. 2018;4(1):18008. doi:10.1038/nrdp.2018.8

32. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/s0140-6736(18)32279-7

33. Quidé Y, Tozzi L, Corcoran M, Cannon DM, Dauvermann MR. The Impact of Childhood Trauma on Developing Bipolar Disorder: Current Understanding and Ensuring Continued Progress. *Neuropsychiatr Dis Treat*. 2020;16:3095-3115. doi:10.2147/ndt.s285540

34. Michalak EE, Murray G, Young AH, Lam RW. Burden of bipolar depression: impact of disorder and medications on quality of life. *CNS Drugs*. 2008;22(5):389-406. doi:10.2165/00023210-200822050-00003

35. Suppes T, Leverich GS, Keck PE Jr, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord*. 2001;67(1-3):45-59. doi:10.1016/s0165-0327(01)00432-3

36. Träger C, Decker L, Wæhrens EE, Knorr U, Miskowiak K, Vinberg M. Influences of patient informed cognitive complaints on activities of daily living in patients with bipolar disorder. An exploratory cross-sectional study. *Psychiatry Res*. 2017;249:268-274. doi:10.1016/j.psychres.2016.12.058

37. Marwaha S, Durrani A, Singh S. Employment outcomes in people with bipolar disorder: a systematic review. *Acta Psychiatr Scand*. 2013;128(3):179-193. doi:10.1111/acps.12087

38. Lima IMM, Peckham AD, Johnson SL. Cognitive deficits in bipolar disorders: Implications for emotion. *Clin Psychol Rev*. 2018;59:126-136. doi:10.1016/j.cpr.2017.11.006

39. Merikangas KR, Jin R, He JP, et al. Prevalence and Correlates of Bipolar Spectrum Disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011;68(3):241. doi:10.1001/archgenpsychiatry.2011.12

40. Magioncalda P, Martino M. A unified model of the pathophysiology of bipolar disorder. *Mol Psychiatry*. 2021;27(1):41380-41021. doi:10.1038/s41380-021-01091-4

41. Savitz J, Drevets WC. Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev*. 2009;33(5):699-771. doi:10.1016/j.neubiorev.2009.01.004

42. Mechawar N, Savitz J. Neuropathology of mood disorders: do we see the stigmata of inflammation? *Transl Psychiatry*. 2016;6(11):e946. doi:10.1038/tp.2016.212

43. Nikolaus S, Antke C, Müller HW. In vivo imaging of synaptic function in the central nervous system: II. Mental and affective disorders. *Behav Brain Res*. 2009;204(1):32-66. doi:10.1016/j.bbr.2009.06.009

44. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*. 2011;15(10):483-506. doi:10.1016/j.tics.2011.08.003

45. Northoff G, Hirjak D, Wolf RC, Magioncalda P, Martino M. All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. *Mol Psychiatry*. 2021;26(1):92-102. doi:10.1038/s41380-020-0814-5

46. Martino M, Magioncalda P. Tracing the psychopathology of bipolar disorder to the functional architecture of intrinsic brain activity and its neurotransmitter modulation: a three-dimensional model. *Mol Psychiatry*. Published online January 7, 2021. doi:10.1038/s41380-020-00982-2

47. Sayana P, Colpo GD, Simões LR, et al. A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. *J Psychiatr Res*. 2017;92:160-182. doi:10.1016/j.jpsychires.2017.03.018

48. Fernandes BS, Steiner J, Molendijk ML, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry*. 2016;3(12):1147-1156. doi:10.1016/s2215-0366(16)30370-4

49. Réus GZ, Fries GR, Stertz L, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience*. 2015;300:141-154. doi:10.1016/j.neuroscience.2015.05.018

50. Barbosa IG, Rocha NP, Assis F, et al. Monocyte and lymphocyte activation in bipolar disorder: a new piece in the puzzle of immune dysfunction in mood disorders. *Int J Neuropsychopharmacol*. 2014;18(1):pyu021. doi:10.1093/ijnp/pyu021

51. Breunis MN, Kupka RW, Nolen WA, et al. High numbers of circulating activated T cells and raised levels of serum IL-2 receptor in bipolar disorder. *Biol Psychiatry*. 2003;53(2):157-165. doi:10.1016/s0006-3223(02)01452-x

52. Tsai SY, Chen KP, Yang YY, et al. Activation of indices of cell-mediated immunity in bipolar mania. *Biol Psychiatry*. 1999;45(8):989-994. doi:10.1016/s0006-3223(98)00159-0

53. do Prado CH, Rizzo LB, Wieck A, et al. Reduced regulatory T cells are associated with higher levels of Th1/TH17 cytokines and activated MAPK in type 1 bipolar disorder. *Psychoneuroendocrinology*. 2013;38(5):667-676. doi:10.1016/j.psyneuen.2012.08.005

54. Brambilla P, Bellani M, Isola M, et al. Increased M1/decreased M2 signature and signs of Th1/Th2 shift in chronic patients with bipolar disorder, but not in those with schizophrenia. *Transl Psychiatry*. 2014;4(7):e406. doi:10.1038/tp.2014.46

55. Köhler O, Sylvia LG, Bowden CL, et al. White blood cell count correlates with mood symptom severity and specific mood symptoms in bipolar disorder. *Aust N Z J Psychiatry*. 2017;51(4):355-365. doi:10.1177/0004867416644508

56. Wu W, Zheng YL, Tian LP, et al. Circulating T lymphocyte subsets, cytokines, and immune checkpoint inhibitors in patients with bipolar II or major depression: a preliminary study. *Sci Rep*. 2017;7(1):40530. doi:10.1038/srep40530

57. Tsai SY, Chung KH, Chen PH. Levels of interleukin-6 and high-sensitivity C-reactive protein reflecting mania severity in bipolar disorder. *Bipolar Disord*. 2017;19(8):708-709. doi:10.1111/bdi.12570

58. Sexton CE, Mackay CE, Ebmeier KP. A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry*. 2009;66(9):814-823. doi:10.1016/j.biopsych.2009.05.024

59. Vederine FE, Wessa M, Leboyer M, Houenou J. A meta-analysis of whole-brain diffusion tensor imaging studies in bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(8):1820-1826. doi:10.1016/j.pnpbp.2011.05.009

60. Nortje G, Stein DJ, Radua J, Mataix-Cols D, Horn N. Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. *J Affect Disord*. 2013;150(2):192-200. doi:10.1016/j.jad.2013.05.034

61. Wise T, Radua J, Nortje G, Cleare AJ, Young AH, Arnone D. Voxel-Based Meta-Analytical Evidence of Structural Disconnectivity in Major Depression and Bipolar Disorder. *Biol Psychiatry*. 2016;79(4):293-302. doi:10.1016/j.biopsych.2015.03.004

62. Heng S, Song AW, Sim K. White matter abnormalities in bipolar disorder: insights from diffusion tensor imaging studies. *J Neural Transm*. 2010;117(5):639-654. doi:10.1007/s00702-010-0368-9

63. Favre P, for the ENIGMA Bipolar Disorder Working Group, Pauling M, et al. Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega- and meta-analyses across 3033 individuals. *Neuropsychopharmacol*. 2019;44(13):2285-2293. doi:10.1038/s41386-019-0485-6

64. Yeo BTT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125-1165. doi:10.1152/jn.00338.2011

65. Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr*. 2008;13(8):663-681. doi:10.1017/s1092852900013754

66. Pani L, Porcella A, Gessa GL. The role of stress in the pathophysiology of the dopaminergic system. *Mol Psychiatry*. 2000;5(1):14-21. doi:10.1038/sj.mp.4000589

67. Lanfumey L, Mongeau R, Cohen-Salmon C, Hamon M. Corticosteroid-serotonin interactions in the neurobiological mechanisms of stress-related disorders. *Neurosci Biobehav Rev*. 2008;32(6):1174-1184. doi:10.1016/j.neubiorev.2008.04.006

68. Martino M, Magioncalda P, Huang Z, et al. Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. *Proc Natl Acad Sci USA*. 2016;113(17):4824-4829. doi:10.1073/pnas.1517558113

69. Conio B, Martino M, Magioncalda P, et al. Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. *Mol Psychiatry*. 2020;25(1):82-93. doi:10.1038/s41380-019-0406-4

70. Greene M, Yan T, Chang E, Hartry A, Touya M, Broder MS. Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. *J Med Econ*. 2018;21(2):127-134. doi:10.1080/13696998.2017.1379412

71. Kondej M, Stępnicki P, Kaczor AA. Multi-Target Approach for Drug Discovery against Schizophrenia. *Int J Mol Sci*. 2018;19(10):3105. doi:10.3390/ijms19103105

72. Girdler SJ, Confino JE, Woesner ME. Exercise as a Treatment for Schizophrenia: A Review. *Psychopharmacol Bull*. 2019;49(1):56-69.

73. Nucifora FC Jr, Woznica E, Lee BJ, Cascella N, Sawa A. Treatment resistant schizophrenia: Clinical, biological, and therapeutic perspectives. *Neurobiol Dis*. 2019;131:104257. doi:10.1016/j.nbd.2018.08.016

74. Stępnicki P, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. *Mol Basel Switz*. 2018;23(8):2087. doi:10.3390/molecules23082087

75. Lau CI, Wang HC, Hsu JL, Liu ME. Does the dopamine hypothesis explain schizophrenia? *Rev Neurosci*. 2013;24(4):389-400. doi:10.1515/revneuro-2013-0011

76. Carlsson A, Lindqvist M. Effect of Chlorpromazine or Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain. *Acta Pharmacol Toxicol (Copenh)*. 2009;20(2):140-144. doi:10.1111/j.1600-0773.1963.tb01730.x

77. Möller HJ. Risperidone: a review. *Expert Opin Pharmacother*. 2005;6(5):803-818. doi:10.1517/14656566.6.5.803

78. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacol*. 2003;28(8):1400-1411. doi:10.1038/sj.npp.1300203

79. Pajonk FG, Wobrock T, Gruber O, et al. Hippocampal Plasticity in Response to Exercise in Schizophrenia. *Arch Gen Psychiatry*. 2010;67(2):133-143. doi:10.1001/archgenpsychiatry.2009.193

80. Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Aust NZ J Psychiatry*. 1999;33(5):349-352. doi:10.1080/j.1440-1614.1999.06241.x

81. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306-1315. doi:10.1016/s0140-6736(11)60873-8

82. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry*. 2019;24(2):198-217. doi:10.1038/s41380-018-0044-2

83. Yildiz A, Vieta E, Leucht S, Baldessarini RJ. Efficacy of Antimanic Treatments: Meta-analysis of Randomized, Controlled Trials. *Neuropsychopharmacol*. 2011;36(2):375-389. doi:10.1038/npp.2010.192

84. Baldessarini RJ, Salvatore P, Khalsa HMK, et al. Morbidity in 303 first-episode bipolar I disorder patients. *Bipolar Disord*. 2010;12(3):264-270. doi:10.1111/j.1399-5618.2010.00812.x

85. Forte A, Baldessarini RJ, Tondo L, Vázquez GH, Pompili M, Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J Affect Disord*. 2015;178:71-78. doi:10.1016/j.jad.2015.02.011

86. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders. *Am J Psychiatry*. 2013;170(11):1249-1262. doi:10.1176/appi.ajp.2013.13020185

87. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition Recommendations from the British Association for Psychopharmacology. *J Psychopharmacol Oxf Engl*. 2016;30(6):495-553. doi:10.1177/0269881116636545

88. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. *J Clin Psychiatry*. 2007;68(03):380-383. doi:10.4088/jcp.v68n0304

89. Terao T, Ishida A, Kimura T, Yarita M, Hara T. Preventive Effects of Lamotrigine in Bipolar II Versus Bipolar I Disorder. *J Clin Psychiatry*. 2017;78(8):e1000-e1005. doi:10.4088/jcp.16m11404

90. Gold AK, Ornelas AC, Cirillo P, et al. Clinical applications of transcranial magnetic stimulation in bipolar disorder. *Brain Behav*. 2019;9(10):e01419. doi:10.1002/brb3.1419

91. Alkermes Announces FDA Approval of LYBALVITM for the Treatment of Schizophrenia and Bipolar I Disorder | BioSpace. Accessed September 7, 2021. https://www.biospace.com/article/releases/alkermes-announces-fda-approval-of-lybalvi-for-the-treatment-of-schizophrenia-and-bipolar-i-disorder/

92. Sun L, McDonnell D, Liu J, von Moltke L. Effect of Food on the Pharmacokinetics of a Combination of Olanzapine and Samidorphan. *Clin Pharmacol Drug Dev*. 2019;8(4):503-510. doi:10.1002/cpdd.688

93. Citrome L, Holt RIG, Walker DJ, Hoffmann VP. Weight gain and changes in metabolic variables following olanzapine treatment in schizophrenia and bipolar disorder. *Clin Drug Investig*. 2011;31(7):455-482. doi:10.2165/11589060-000000000-00000

94. Cunningham JI, Eyerman DJ, Todtenkopf MS, et al. Samidorphan mitigates olanzapine-induced weight gain and metabolic dysfunction in rats and non-human primates. *J Psychopharmacol Oxf Engl*. 2019;33(10):1303-1316. doi:10.1177/0269881119856850

95. Buchanan RW. How Much of an Advance Is the Addition of Samidorphan to Olanzapine? *Am J Psychiatry*. 2020;177(12):1113-1114. doi:10.1176/appi.ajp.2020.20091425

96. Lord CC, Wyler SC, Wan R, et al. The atypical antipsychotic olanzapine causes weight gain by targeting serotonin receptor 2C. *J Clin Invest*. 2017;127(9):3402-3406. doi:10.1172/jci93362

97. Effects of Olanzapine and Haloperidol on the Metabolic Status of Healthy Men. *J Clin Endocrinol Metab*. 2010;95(1). doi:10.1210/jc.2008-1815

98. Silverman BL, Martin W, Memisoglu A, DiPetrillo L, Correll CU, Kane JM. A randomized, double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophr Res*. 2018;195:245-251. doi:10.1016/j.schres.2017.10.014

99. Martin WF, Correll CU, Weiden PJ, et al. Mitigation of Olanzapine-Induced Weight Gain With Samidorphan, an Opioid Antagonist: A Randomized Double-Blind Phase 2 Study in Patients With Schizophrenia. *Am J Psychiatry*. 2019;176(6):457-467. doi:10.1176/appi.ajp.2018.18030280

100. Prescribing information for LYBALVI. Accessed September 7, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213378s000lbl.pdf

101. Thomas K, Saadabadi A. Olanzapine. In: StatPearls. StatPearls Publishing; 2021. Accessed September 7, 2021. http://www.ncbi.nlm.nih.gov/books/NBK532903/

102. Del Fabro L, Delvecchio G, D'Agostino A, Brambilla P. Effects of olanzapine during cognitive and emotional processing in schizophrenia: A review of functional magnetic resonance imaging findings. *Hum Psychopharmacol Clin Exp*. 2019;34(3):e2693. doi:10.1002/hup.2693

103. Chaudhary AMD, Khan MF, Dhillon SS, Naveed S. A Review of Samidorphan: A Novel Opioid Antagonist. *Cureus*. 2019;11(7):e5139. doi:10.7759/cureus.5139

104. Cunningham JI, Todtenkopf MS, Dean RL, et al. Samidorphan, an opioid receptor antagonist, attenuates drug-induced increases in extracellular dopamine concentrations and drug self-administration in male Wistar rats. *Pharmacol Biochem Behav*. 2021;204:173157. doi:10.1016/j.pbb.2021.173157

105. Smith KL, Cunningham JI, Eyerman DJ, Dean RL III, Deaver DR, Sanchez C. Opioid system modulators buprenorphine and samidorphan alter behavior and extracellular neurotransmitter concentrations in the Wistar Kyoto rat. *Neuropharmacology*. 2019;146:316-326. doi:10.1016/j.neuropharm.2018.11.015

106. Sun L, McDonnell D, von Moltke L. Pharmacokinetics and Short-term Safety of ALKS 3831, a Fixed-dose Combination of Olanzapine and Samidorphan, in Adult Subjects with Schizophrenia. *Clin Ther*. 2018;40(11):1845-1854.e2. doi:10.1016/j.clinthera.2018.09.002

107. Sun L, von Moltke L, Rowland Yeo K. Physiologically-Based Pharmacokinetic Modeling for Predicting Drug Interactions of a Combination of Olanzapine and Samidorphan. *CPT Pharmacomet Syst Pharmacol*. 2020;9(2):106-114. doi:10.1002/psp4.12488

108. Lowe EJ, Ackman ML. Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment. *Ann Pharmacother*. 2010;44(4):727-732. doi:10.1345/aph.1m398

109. Sun L, Mills R, Sadler BM, Rege B. Population Pharmacokinetics of Olanzapine and Samidorphan When Administered in Combination in Healthy Subjects and Patients With Schizophrenia. *J Clin Pharmacol*. 2021;61(11):1430-1441. doi:10.1002/jcph.1911

110. Sun L, Yagoda S, Du Y, von Moltke L. Effect of hepatic and renal impairment on the pharmacokinetics of olanzapine and samidorphan given in combination as a bilayer tablet. *Drug Des Devel Ther*. 2019;13:2941-2955. doi:10.2147/dddt.s205000

111. Citrome L, Graham C, Simmons A, et al. A Combination of Olanzapine and Samidorphan in Adults with Schizophrenia and Bipolar I Disorder: Overview of Clinical Data. *CNS Spectr*. 2021;26(2):170-170. doi:10.1017/s1092852920002771

112. Potkin SG, Kunovac J, Silverman BL, et al. Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia: Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study. *J Clin Psychiatry*. 2020;81(2):19m12769. doi:10.4088/jcp.19m12769

113. Simmons A, Carpenter-Conlin J, Bessonova L, et al. Qualitative Clinical Trial Exit Interviews Evaluating Treatment Benefit, Burden, and Satisfaction in Patients with Schizophrenia. *CNS Spectr*. 2021;26(2):156-157. doi:10.1017/s1092852920002503

114. Yagoda S, Graham C, Simmons A, Arevalo C, Jiang Y, McDonnell D. Long-term safety and durability of effect with a combination of olanzapine and samidorphan in patients with schizophrenia: results from a 1-year open-label extension study. *CNS Spectr*. 2021;26(4):383-392. doi:10.1017/s1092852920001376

115. Srisurapanont M, Suttajit S, Likhitsathian S, Maneeton B, Maneeton N. A meta-analysis comparing short-term weight and cardiometabolic changes between olanzapine/samidorphan and olanzapine. *Sci Rep*. 2021;11(1):7583. doi:10.1038/s41598-021-87285-w

116. Correll CU, Newcomer JW, Silverman B, et al. Effects of Olanzapine Combined With Samidorphan on Weight Gain in Schizophrenia: A 24-Week Phase 3 Study. *Am J Psychiatry*. 2020;177(12):1168-1178. doi:10.1176/appi.ajp.2020.19121279

117. Kahn RS, Silverman BL, DiPetrillo L, et al. A phase 3, multicenter study to assess the 1-year safety and tolerability of a combination of olanzapine and samidorphan in patients with schizophrenia: results from the ENLIGHTEN-2 long-term extension. *Schizophr Res*. 2021;232:45-53. doi:10.1016/j.schres.2021.04.009

118. Kahn R, Silverman B, DiPetrillo L, et al. Phase 3 Safety and Tolerability Results of the Combination Olanzapine and Samidorphan in Patients with Schizophrenia: The 1 Year ENLIGHTEN-2-Extension. *CNS Spectr*. 2021;26(2):155-156. doi:10.1017/s1092852920002485

119. Sun L, McDonnell D, Liu J, von Moltke L. Bioequivalence of Olanzapine Given in Combination With Samidorphan as a Bilayer Tablet (ALKS 3831) Compared With Olanzapine-Alone Tablets: Results From a Randomized, Crossover Relative Bioavailability Study. *Clin Pharmacol Drug Dev*. 2019;8(4):459-466. doi:10.1002/cpdd.601

120. Sun L, Yagoda S, Yao B, Graham C, von Moltke L. Combination of Olanzapine and Samidorphan Has No Clinically Significant Effect on the Pharmacokinetics of Lithium or Valproate. *Clin Drug Investig*. 2020;40(1):55-64. doi:10.1007/s40261-019-00860-y

121. Sun L, Yagoda S, Xue H, et al. Combination of olanzapine and samidorphan has no clinically relevant effects on ECG parameters, including the QTc interval: results from a phase 1 QT/QTc study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;100:109881. doi:10.1016/j.pnpbp.2020.109881

122. Brunette MF, Correll CU, O'Malley SS, et al. Olanzapine Plus Samidorphan (ALKS 3831) in Schizophrenia and Comorbid Alcohol Use Disorder: A Phase 2, Randomized Clinical Trial. *J Clin Psychiatry*. 2020;81(2):19m12786. doi:10.4088/jcp.19m12786